Contents

Low-Dose Buprenorphine in Severe Interpersonal and Affective Dysregulation

A Primary Care Consideration Guide

This document is an informational summary of emerging clinical rationale. It does not constitute a standard of care, clinical protocol, or medical advice. It is intended to support clinician-patient conversation and shared decision-making. Patients may bring this document to appointments for discussion.

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1. Purpose and Scope

1.1 Intended Audience and Scope

This guide is written for primary care clinicians (PCPs) who encounter patients with borderline personality disorder (BPD) or BPD-spectrum presentations — conditions fundamentally characterized by interpersonal dysregulation — and who are considering whether low-dose buprenorphine may be appropriate to discuss or trial in select cases.

The evidence base for this application remains limited. The goal of this document is not to advocate for routine prescribing, but to provide a structured framework for clinicians who are already comfortable with buprenorphine and who want to understand the emerging rationale, relevant clinical scenarios, and practical considerations. Familiarity with buprenorphine prescribing — whether through opioid use disorder (OUD) treatment or pain management — is assumed.

The tone throughout is intentionally cautious. Language such as "may," "hypothesized," and "emerging evidence" reflects the current state of the literature. Clinicians should exercise independent judgment and consult relevant specialists when uncertainty is high.

1.2 Legal and Regulatory Considerations (US concern, addressing DEA)

Buprenorphine is Schedule III. As of 2023, the DEA X-waiver requirement has been eliminated, and any DEA-registered practitioner with Schedule III prescribing authority may prescribe buprenorphine, including for opioid use disorder, without additional certification. Off-label prescribing for non-OUD indications remains legally permissible when based on clinical judgment, with documentation of rationale. Careful documentation of treatment resistance, risk assessment, and functional goals is recommended.

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2. Clinical Context in Primary Care

2.1 BPD in Primary Care Settings

Borderline personality disorder affects approximately 1–2% of the general population, with substantially higher prevalence in clinical settings — estimates range from 6% in primary care to 10–20% in psychiatric inpatient contexts. Many patients with BPD present to primary care before receiving a formal psychiatric diagnosis, and many never receive one at all, particularly in underserved settings.

BPD is diagnosed significantly more often in women, but epidemiological data suggest the true prevalence is more evenly distributed. Differential diagnosis rates likely reflect clinical bias and variation in how dysregulation presents across populations rather than true sex-based differences in prevalence. Clinicians should not assume this presentation is uncommon in patients who are not women.

The clinical burden in primary care is significant. BPD carries high rates of comorbidity with chronic pain conditions, substance use disorders, mood and anxiety disorders, and trauma-related presentations. Patients with BPD are disproportionately high utilizers of healthcare — including emergency departments, urgent care, and crisis services — and care is frequently fragmented across providers who may not share diagnostic information or treatment goals.

2.2 The Core Interpersonal Dysregulation

While BPD presents with affective instability, impulsivity, identity disturbance, and other features, the core dysregulation is interpersonal. Patients with BPD experience intense emotional reactions to real or perceived changes in closeness, connection, or availability of important others. Abandonment — whether actual or feared — triggers cascading affective and behavioral responses that can be severe and destabilizing.

These interpersonal crises often occur outside of clinical settings and may not be directly visible to PCPs. What PCPs observe are the downstream effects:

- Somatic complaints that escalate during periods of interpersonal stress
- Crisis visits or after-hours contact following relationship ruptures
- Requests for medication changes driven by acute relational distress rather than sustained medication inefficacy
- Difficulty maintaining consistent therapeutic relationships or follow-up appointments
- Treatment refusal or disengagement that may itself be driven by attachment-related anxiety

Severe interpersonal dysregulation can impair continuity of care. Patients in the grip of intense attachment-related distress may disengage, no-show, or present in ways that complicate clinical management. Interventions that address the underlying interpersonal regulatory system may therefore have benefits that extend beyond symptom relief to improved clinical engagement and care continuity.

3. The Endogenous Opioid System and Interpersonal Neurobiology

3.1 Opioid Signaling, Attachment, and Social Pain

The endogenous opioid system plays a well-established role in the regulation of physical pain, but it is also critically involved in social bonding, attachment, separation distress, and the emotional response to interpersonal loss. This connection is not metaphorical — preclinical and clinical research demonstrates that the experience of social rejection activates overlapping neural substrates with physical pain, and that endogenous opioid signaling modulates both.

The opioid system is central to mammalian attachment. Opioid release reinforces proximity to attachment figures; opioid withdrawal occurs during separation. The distress of social loss — what we might call psychological or emotional pain — is mediated in part by reduced opioid tone. This framework, developed extensively in the work of Jaak Panksepp and others, positions the opioid system as a core neurobiological substrate of social connection.

It is also important to recognize that interpersonal and affective dysregulation is not unique to categorical BPD. Trauma-spectrum disorders, complex PTSD, and other chronic stress exposures are associated with alterations in endogenous opioid signaling and attachment-related neurobiology. The mechanistic model described here may therefore extend beyond strict DSM diagnostic boundaries to trauma-spectrum presentations — including complex PTSD — where interpersonal and affective dysregulation is the core clinical feature. However, the direct evidence reviewed in this document, including the Yovell trial and the neuropeptide model literature, specifically addresses BPD populations. Whether equivalent endogenous opioid dysregulation underlies CPTSD presentations is biologically plausible but not yet well-established. Careful clinical formulation — rather than rigid categorical diagnosis — should guide application, and clinicians should be transparent with patients about the degree to which evidence applies to their specific presentation.

Research in BPD specifically has identified evidence of reduced baseline endogenous opioid tone in this population. Barbara Stanley and colleagues, in their work on the neuropeptide model of BPD (*The Interpersonal Dimension of Borderline Personality Disorder: Towards a Neuropeptide Model*), propose that dysregulation of the endogenous opioid system is central to BPD pathophysiology and explicitly suggest that buprenorphine warrants investigation as a treatment.

Bandelow's work (*Borderline Personality Disorder: A Dysregulation of the Endogenous Opioid System?*) further develops this hypothesis by conceptualizing a range of BPD symptoms as potential regulatory responses to a dysregulated endogenous opioid system. In this model, chronic emptiness and anhedonia may reflect reduced baseline opioid tone; frantic efforts to avoid abandonment and heightened attachment behaviors may represent attempts to access the rewarding effects of social bonding; substance use directly targets opioid signaling; and behaviors such as self-injury, aggression, food restriction, and sensation seeking may function as rapid methods of endogenous opioid activation. Rather than viewing these behaviors solely as impulsive or self-destructive

alone, this framework interprets them as biologically mediated efforts to regulate affect within a maladaptive opioid system.

3.2 A Hypothesized Reinforcement and Regulatory Loop

Based on the above, the following mechanistic hypothesis is proposed: in individuals with reduced baseline opioid tone, interpersonal stressors — particularly those involving separation, rejection, or loss of connection — produce affective surges of disproportionate magnitude. These states may then be followed by partial relief through endogenous opioid release, whether through resolution of the stressor, self-injurious behavior, or other high-intensity affective or behavioral states. This creates a reinforcement cycle that maintains both the intensity of interpersonal reactions and the reliance on maladaptive regulatory behaviors.

If this model is correct, pharmacological interventions that raise baseline opioid tone and simultaneously attenuate the reinforcing surge may reduce both the frequency of interpersonal crises and the reliance on behaviors that previously served a regulatory function.

This model is speculative and has not been formally tested in prospective clinical trials designed for this purpose. It is offered as a heuristic for understanding why opioid-based pharmacological approaches might produce interpersonal and affective stabilization in BPD.

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4. Buprenorphine Pharmacology Relevant to Interpersonal and Affective Modulation

4.1 Relevant Pharmacological Properties

Buprenorphine has several pharmacological properties that distinguish it from both full opioid agonists and other analgesics, and that are directly relevant to its potential role in modulating interpersonal and affective dysregulation:

Partial μ-opioid receptor agonist with high receptor affinity. Buprenorphine binds to μ-opioid receptors with very high affinity — meaning it occupies the receptors strongly and displaces other opioids — but activates them with submaximal efficacy. This combination produces two therapeutically relevant effects: (1) it raises baseline opioid tone in a controlled, steady way, and (2) it attenuates the reinforcing opioid surge from endogenous release (such as following self-injury or intense affective states), because the receptors are already occupied by buprenorphine. Additionally, the submaximal efficacy creates a ceiling effect on respiratory depression, making buprenorphine substantially safer than full agonists. At low doses, the primary therapeutic action is likely receptor stabilization and blockade of endogenous surges, rather than direct agonist effects.

κ-opioid receptor antagonist. This property deserves particular emphasis. κ-opioid receptors are strongly implicated in the experience of dysphoria, stress-induced nega-

tive affect, aversion, and suicidal ideation. Endogenous κ-opioid signaling is activated by stress and contributes to the negative emotional valence that follows aversive experiences, including interpersonal rejection or loss. By blocking κ receptors, buprenorphine may reduce the intensity and duration of both stress-induced dysphoria and suicidal states — an effect distinct from its μ-agonist activity and potentially central to its relevance in both BPD and suicidality more broadly. Research by Carlezon, Bruchas, and others has characterized the κ-opioid system's role in mood and stress regulation in considerable depth.

Lower misuse potential. Relative to full opioid agonists, buprenorphine's partial agonism and ceiling effects reduce reinforcing properties at higher doses, and its high receptor affinity limits displacement by other opioids.

4.2 Core Clinical Hypothesis

Buprenorphine at low doses may function as a baseline opioid tone stabilizer — partially correcting a hypothesized deficit in endogenous opioid signaling — while simultaneously occupying μ-receptors in a way that attenuates the reinforcing opioid surge that follows high-intensity affective or behavioral states (including self-injury, interpersonal crises, or other stress-driven behaviors). By raising the baseline and flattening the peaks, buprenorphine may reduce both the need for and the reward value of maladaptive regulatory behaviors. Additionally, through κ-receptor antagonism, buprenorphine may reduce stress-induced dysphoria and suicidal ideation. The combined effect may result in more proportional emotional responses to interpersonal stressors, with reduced frequency and intensity of affective crises and reduced reliance on behaviors that previously served a regulatory function.

This is the central claim of this document. It is supported by emerging evidence and plausible mechanistic reasoning. It is not established as standard of care.

4.3 Note on Dissociative Symptoms

Dissociative symptoms — including depersonalization, derealization, and amnestic episodes — frequently co-occur with BPD-spectrum presentations and may be underrecognized in primary care settings. The endogenous opioid system has been implicated in dissociative processes, and clinicians initiating opioid modulation should monitor for changes in dissociative symptoms, particularly in patients with known or suspected dissociative disorders.

In patients with prominent dissociative symptoms, the choice of formulation may be worth considering. Continuous, low-level transdermal delivery theoretically minimizes abrupt changes in receptor occupancy compared to intermittent sublingual dosing, which may be relevant in patients whose dissociative symptoms fluctuate with peak–trough pharmacokinetic variation. However, empirical data comparing formulations specifically in dissociative populations are limited, and this consideration remains theoretical.

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5. Clinical Scenarios Where Consideration May Arise

The following scenarios represent contexts in which the question of buprenorphine for interpersonal and affective dysregulation is most likely to arise in primary care. They are arranged to reflect both clinical appropriateness and prescribing infrastructure.

Scenario A: Comorbid Opioid Use Disorder

This is the most straightforward scenario. Buprenorphine is standard of care for OUD, and PCPs with buprenorphine prescribing capacity are already authorized to provide it. For patients with both OUD and significant interpersonal or affective dysregulation or BPD, dual benefit is plausible and worth monitoring prospectively. Clinicians should document affective and interpersonal outcomes alongside OUD-related outcomes and consider whether titration decisions might be informed by both.

When co-occurring OUD is present, standard evidence-based OUD dosing and monitoring protocols apply. The considerations in this document are specific to patients without active opioid use disorder or to those whose OUD is already being managed according to established guidelines.

Scenario B: Comorbid Chronic Pain and Interpersonal/Affective Dysregulation

Chronic pain is highly comorbid with BPD, and this comorbidity is frequently underrecognized and undertreated. Patients with BPD face significant stigma in pain management settings, and their reports of pain may be dismissed or attributed to emotional dysregulation rather than nociceptive pathology. This can lead to inadequate pain treatment that itself contributes to emotional instability.

In patients with legitimate chronic pain needs and concurrent interpersonal or affective dysregulation, buprenorphine may offer dual nociceptive and affective modulation. Buprenorphine is an established analgesic (including via transdermal formulation for chronic pain), and initiating it for pain with attention to interpersonal and affective outcomes is a reasonable clinical approach. Clinicians should be explicit in their documentation about the indication(s) being addressed.

Scenario C: Early Intervention in Diagnosed BPD with Prominent Interpersonal Dysregulation

For patients with a clear BPD diagnosis (or well-characterized BPD-spectrum presentation) whose primary clinical feature is interpersonal dysregulation — intense reactions to perceived abandonment, unstable relationships, difficulty maintaining therapeutic alliances — buprenorphine may be considered as a primary pharmacological intervention without requiring trials of medications that do not target the endogenous opioid system.

This approach is based on the following rationale:

- The endogenous opioid system is central to social bonding, attachment, and separation distress — the domains most affected in BPD

- Medications such as SSRIs, mood stabilizers, and antipsychotics have limited efficacy in BPD and do not directly modulate opioid signaling
- Requiring patients to "fail" medications that don't target the relevant neurobiology delays access to potentially effective treatment and prolongs suffering
- Interpersonal dysregulation itself impairs treatment engagement; addressing it pharmacologically may improve the patient's ability to participate in psychotherapy and collaborate with providers

Clinical prerequisites for this approach:

- Clear diagnostic assessment (ideally with psychiatric consultation, though this may occur after initiating if access is limited)
- Documented interpersonal pattern consistent with BPD (not just affective symptoms)
- Informed consent discussion emphasizing off-label use and emerging evidence base
- Plan for psychotherapy referral or engagement (even if not yet achieved)
- Structured follow-up and monitoring plan (see Section 7.2)

This is a more assertive clinical stance and will be appropriate for clinicians who are comfortable with the mechanistic rationale and who have experience managing BPD presentations. It reflects the position that if we believe the opioid system is core to BPD pathophysiology, we should not require patients to demonstrate treatment failure on irrelevant medications before addressing it.

Patients with significant dissociative symptoms may be particularly sensitive to changes in opioid tone. If dissociation is prominent, transdermal delivery may be preferable to sublingual dosing, as continuous low-level absorption produces fewer fluctuations in receptor occupancy than intermittent peak-trough kinetics. The Dissociative Experiences Scale-II (DES-II) can help identify these patients prior to initiating.[1]

Scenario D: Severe Treatment-Resistant Affective Dysregulation (Conservative Approach)

For clinicians who prefer a more conservative framework, the following represents an alternative entry point. The relevant patient has:

- A diagnosis of BPD or a well-characterized BPD-spectrum presentation
- Active engagement in evidence-based psychotherapy (ideally DBT or a structured derivative)
- Trials of two or more pharmacological agents with established use in BPD (e.g., SSRIs, mood stabilizers, low-dose antipsychotics) without adequate response
- Persistent crisis cycling — including frequent ER presentations, self-injury, or repeated acute decompensations — despite the above

[1] Carlson, E. B., & Putnam, F. W. (1993). An update on the Dissociative Experiences Scale. *Dissociation: Progress in the Dissociative Disorders, 6*(1), 16–27. The DES-II is freely available online at https://traumadissociation.com/des.

In this setting, buprenorphine may warrant consideration. Clinicians should ensure that psychiatric consultation has been obtained or attempted, that the patient has been engaged in shared decision-making, and that adequate documentation of the treatment rationale is present in the chart.

Note: This framework positions buprenorphine as a "last resort" after other treatments have failed. However, it should be recognized that the medications being used as comparators (SSRIs, mood stabilizers, antipsychotics) do not target the endogenous opioid system and have limited evidence of efficacy in BPD. The lack of response to these agents may not indicate treatment resistance so much as the absence of a treatment that addresses the core neurobiological dysregulation. Scenario C reflects this reasoning more directly.

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6. Evidence Anchors

6.1 The Yovell Trial

The most directly relevant controlled clinical evidence comes from a randomized controlled trial by Yovell et al. (2015), *"Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation."* In this trial, opioid-naive patients with severe suicidal ideation were randomized to ultra-low-dose buprenorphine (starting at 0.1–0.2 mg sublingual once or twice daily) or placebo. The primary finding was rapid and significant reduction in suicidal ideation in the buprenorphine group.

A post-hoc analysis of the BPD subgroup within the trial showed a particularly robust treatment effect: BPD patients on buprenorphine showed substantially greater improvement than BPD patients on placebo. This subgroup finding was unplanned and should be interpreted with appropriate caution — it was not powered or designed to test this comparison specifically. Nevertheless, it represents the strongest available controlled clinical signal supporting the application described in this guide, and the direction and magnitude of the effect are notable.

The doses used in the Yovell trial — 0.1 to 0.2 mg starting dose, with titration as needed — are far below the 2–16 mg range typically used in OUD treatment. This distinction is clinically important: prescribing at these doses is not equivalent to OUD treatment and should not be framed as such to patients or in documentation.

6.2 Case Report: Buprenorphine/Naloxone for BPD

A published case report — *"The Use of Buprenorphine/Naloxone to Treat Borderline Personality Disorder"* — describes an opioid-naive patient with BPD who was initiated on buprenorphine/naloxone and titrated to clinical response. The severity of her presentation before treatment warrants emphasis: from 2017 to March 2020 she had 18 emergency department visits with 9 inpatient admissions, and her average time in hospital per visit (including both ED and inpatient) was 216.4 hours.

Treatment was initiated in March 2020 at 2 mg, escalated to 4 mg in April, and to 6 mg in October. The outcome data are striking. Comparing the 15 months before buprenorphine to the 15 months after, crisis service contacts fell from 41 to 12 events. Following the dose increase to 6 mg in October, she accessed crisis services not at all. Over a longer window — 39 months pre-treatment versus 13 months post-initiation — hospital-based crisis utilization also showed substantial reduction: average time in hospital per visit dropped from 216.4 hours to 13.7 hours, admissions per year decreased from 2.8 to 1.8, and average length of admission decreased from 401.2 hours to 63 hours.

Notably, during preparation of the manuscript, the patient discontinued the medication briefly. She was hospitalized with suicidal ideation and emotional dysregulation consistent with her pre-treatment baseline; these resolved when she resumed buprenorphine. This discontinuation-and-recurrence sequence, while a single observation, further strengthens the available naturalistic evidence that the clinical improvement was attributable to the medication rather than to concurrent life changes.

Several features of this case are clinically instructive:

- **Starting dose:** The prescriber initiated at 2 mg — the lowest commercially available sublingual tablet — rather than at the ultra-low doses used in the Yovell protocol. This is a pragmatic approach that avoids the need for compounding or patient-prepared dilution and is consistent with standard buprenorphine tablet availability.
- **Titration endpoint:** Dose increases were guided by a concrete functional outcome (frequency of crisis calls) rather than symptom self-report alone, which is consistent with best practices for this population.
- **Maintenance dose:** The stabilization dose of 6 mg falls below standard OUD treatment ranges (typically 8–24 mg) but substantially above the ultra-low-dose range of the Yovell trial. This suggests that some patients with BPD may require doses in an intermediate range — above what ultra-low-dose protocols specify, but well below OUD treatment thresholds.
- **Formulation:** Buprenorphine/naloxone was used rather than buprenorphine monotherapy. In an opioid-naive patient, this is a reasonable choice given its wider availability, lower diversion risk, and the fact that naloxone has negligible sublingual bioavailability and is unlikely to meaningfully alter the clinical effect in the absence of parenteral administration.

This case report must be interpreted with significant caution. A single case cannot establish efficacy, generalizability, or an optimal dose range. It does not supersede or contradict the Yovell protocol; rather, it extends the observable clinical range and suggests that effective doses may vary substantially across individuals. The appropriate inference is not that 2–6 mg is a target range, but that some patients may not respond adequately to ultra-low doses and may benefit from careful titration into a higher sub-OUD range, guided by functional outcomes and monitored closely.

Taken together, the Yovell trial and this case report bracket a preliminary dose range of approximately 0.1–6 mg for this indication — with the strong caveat that the entire evidence base consists of one controlled trial with a post-hoc BPD subgroup finding

and a single case report. Clinicians should treat this range as hypothesis-generating, not prescriptive.

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7. Dosing Considerations, Risk Mitigation, and Monitoring Protocol

7.1 Dosing Framework

The following represents a reasonable framework for buprenorphine in interpersonal and affective dysregulation, informed by the Yovell protocol, the published case report, and clinical judgment. It is not a fixed protocol and should be individualized based on clinical context.

Buprenorphine in this context is intended as a scheduled, baseline-modulating medication. It is not intended as a PRN agent for acute emotional relief. Prescribing should not frame it as providing immediate emotional suppression or as a crisis intervention tool.

Starting dose: 0.1–0.2 mg sublingual once or twice daily. This starting range is consistent with the Yovell protocol and with the tolerability profile of opioid-naive patients. Opioid-naive individuals are often highly sensitive to buprenorphine at commercially available doses — nausea and vomiting are commonly reported at 2 mg in opioid-naive people — and a poor early experience at too high a dose may cause a patient to abandon a medication that could have worked at a lower one. Starting low is not merely cautious; it is clinically important for this population. Commercial tablets are not available below 2 mg, so ultra-low-dose initiation requires either compounding or patient-prepared dilution (see below).

Titration: Titration should be slow, guided by functional response rather than subjective mood reports alone, and informed by concrete behavioral endpoints where possible (e.g., frequency of crisis contacts, therapy attendance, self-injury frequency). Dose increments should be conservative — 0.1–0.2 mg at a time — with adequate time at each dose to assess response before escalating. In patients with cyclical estrogen fluctuation, apparent dose insufficiency during low-estrogen phases does not necessarily indicate tolerance or the need for a permanent dose increase. (See Section 7.2, Cyclical Estrogen Fluctuation.)

Expected response range: The majority of controlled evidence — including the Yovell trial — suggests that many opioid-naive patients may demonstrate meaningful affective stabilization within approximately 0.1–1 mg daily. This should be the primary expectation when initiating, and clinicians should not assume that higher doses are necessary before an adequate low-dose trial has been completed.

For patients with more severe BPD presentations, significant treatment resistance, or established opioid tolerance who do not achieve adequate functional stabilization within the low-dose range, careful titration to higher sub-OUD doses may be warranted. The published case report (Section 6.2) documents stabilization at 6 mg in a refractory patient using a step-wise escalation (2 mg $\rightarrow$ 4 mg $\rightarrow$ 6 mg) driven by persistence of crisis

behaviors — increasing only when a clear functional target remained unmet. This cadence is a reasonable model for refractory titration. Clinicians should reassess carefully before titrating beyond the low-dose range, and escalation should always be driven by observable functional endpoints rather than patient-reported distress alone.

The goal at every stage is the minimum effective dose.

Formulation:

- Sublingual buprenorphine monotherapy (without naloxone) is appropriate in opioid-naive patients at low doses. In patients with OUD or higher misuse risk, buprenorphine/naloxone is standard. If titration into higher sub-OUD doses becomes clinically indicated, buprenorphine/naloxone is also a reasonable formulation choice; in opioid-naive patients, sublingual naloxone has negligible bioavailability and is unlikely to meaningfully alter the clinical effect.
- Transdermal formulations may be considered where continuous low-level exposure is preferred, particularly in patients with prominent dissociative symptoms or sensitivity to pharmacokinetic fluctuation (see Section 4.3). Note that transdermal formulations have a slower onset — patients should be counseled that initial effect may not be noticeable for approximately 12 hours after first application, making this a less suitable choice when there is active affective crisis.

A note on dosing practicalities below 2 mg: Commercial sublingual buprenorphine is available in a lowest dose of 2 mg. For ultra-low-dose initiation (0.1–1 mg), clinicians have two practical options:

Compounding pharmacy: A prescription for the appropriate dose can be sent to a compounding pharmacy. This produces a precise, clinician-specified formulation but is generally not covered by insurance and represents an out-of-pocket cost for the patient.

Patient-prepared sublingual solution: Some clinicians prescribe standard 2 mg sublingual tablets with instructions for the patient to prepare a dilute solution at home. While this approach places more responsibility on the patient and requires a degree of trust in their ability to follow instructions carefully, it is a practical option for reliable patients with whom the clinician has an established relationship. A sample protocol:

- Obtain a small amber glass jar (2 mL capacity) and 1 mL oral syringes
- Use a new, clean 1 mL oral syringe for each dose withdrawal
- Measure 2 mL of distilled water into the jar
- Place one 2 mg buprenorphine tablet into the jar — the tablet dissolves quickly and does not require prolonged waiting
- The resulting solution contains 1 mg per mL; doses can be drawn up precisely using the syringe (e.g., 0.2 mL = 0.2 mg)
- Administer the measured dose sublingually and hold for 5–10 minutes; because the tablet is pre-dissolved, absorption is faster than with solid formulations and prolonged holding is not necessary
- Rinse mouth with water afterward; avoid brushing teeth for at least one hour
- Store prepared solution in the refrigerator in a tightly closed, light-resistant con-

tainer. A beyond-use date of 14 days is appropriate per USP guidance.[2] Keep out of reach of children.
- This preparation is non-sterile and intended for short-term refrigerated use only. Clinicians should document that dilution was performed under instruction and that stability data for buprenorphine in aqueous solution are limited.

At a minimum daily dose of 0.2 mg, one 2 mg tablet prepared in this way will last approximately 10 days — within the 14-day stability window.

When prescribing standard commercial tablets for patient-prepared dilution, clinicians should ensure the chart clearly documents the off-label indication, the intended dose range, and the rationale for dilution rather than commercial low-dose formulation (e.g., cost, insurance coverage, compounding access).

Sublingual administration — whether via commercial tablet or prepared solution — has a relatively rapid onset, with many patients noticing effect within approximately one hour. This makes it preferable to transdermal formulations when prompt symptom relief is clinically indicated.

Note: Naloxone-containing formulations should be avoided in patients with documented hypersensitivity to naloxone or in cases of acute hepatitis or significant hepatic impairment where opioid antagonists may worsen hepatic stress.

7.2 Risk Mitigation and Monitoring Protocol

Because buprenorphine is a Schedule III controlled substance, structured monitoring is essential for safe, transparent, and defensible prescribing.

Baseline Assessment (Prior to Initiation)

PDMP review. Consult the Prescription Drug Monitoring Program to identify concurrent controlled substance prescriptions. Note that naltrexone, including low-dose naltrexone (LDN) formulations, may not appear in all state PDMP databases and should be screened for explicitly during medication reconciliation. **Concurrent use of naltrexone is absolutely contraindicated and will precipitate acute withdrawal.**

Urine drug screen. Obtain baseline toxicology to identify undisclosed opioid or substance use, including substances not captured in prescription databases.

Hepatic risk / LFTs (risk-based). Buprenorphine is hepatically metabolized; exposure increases in moderate–severe hepatic impairment. Consider baseline liver enzymes (and periodic monitoring) in patients with known liver disease or risk factors (e.g., viral hepatitis), and monitor clinically for excess sedation/toxicity in moderate–severe impairment.

Suicide risk assessment. Document baseline suicidal ideation using clinical interview or a structured tool such as the C-SSRS. Given that the strongest controlled clinical evidence for this approach involves suicidality, serial assessment is particularly relevant.

[2] US Pharmacopeial Convention, Inc. *USP Pharmacists' Pharmacopeia.* 2nd ed. Rockville, MD: US Pharmacopeial Convention, Inc; 2008:775–779.

Prior treatment history. Document psychotherapy exposure, prior medication trials and responses, functional impairment, and crisis history. This establishes the rationale for initiating and provides a baseline for measuring response.

Benzodiazepine and CNS depressant review. Concurrent use of benzodiazepines, gabapentinoids (gabapentin, pregabalin), alcohol, or sedating sleep aids significantly increases respiratory depression risk. These are common in the BPD population and may not all appear in the PDMP. Review and document; consider whether tapering or discontinuation is indicated before initiating.

Dissociative symptom screening. Patients with significant dissociation may be more sensitive to fluctuations in opioid tone. Screening with the DES-II prior to initiation can identify patients for whom transdermal formulations may be preferable to sublingual dosing.

Cyclical estrogen fluctuation. In patients who experience cyclical estrogen fluctuation — including those with menstrual cycles and those on estrogen hormone replacement therapies — clinicians should ask whether interpersonal dysregulation or affective intensity tracks hormonal cycle phase. Estrogen upregulates μ-opioid receptor sensitivity, meaning opioid tone varies with estrogen levels. Patients with already-reduced baseline opioid tone may experience compounding deficits during low-estrogen phases. A positive pattern here provides additional mechanistic support for this intervention and helps distinguish later apparent dose insufficiency from true tolerance — premenstrual or low-estrogen-phase breakthrough does not necessarily warrant a permanent dose increase.

History of bipolar spectrum disorder. Data regarding buprenorphine in bipolar populations without OUD are limited. While available evidence does not suggest systematic worsening of psychiatric symptoms, clinicians should monitor for mood destabilization in patients with known bipolar disorder.

Establish measurable treatment goals. Define what response would look like in concrete terms — for example, reduction in suicidal ideation, fewer crisis contacts, improved therapy engagement, or greater relational stability. These goals anchor later reassessment. The case report's use of crisis call frequency as a titration endpoint is a useful model: specific, observable, and not dependent solely on patient self-report.

Structured outcome measures can anchor this assessment. The Zanarini Rating Scale for BPD (ZAN-BPD)[3] is a brief clinician-administered instrument that provides a validated framework for tracking change across BPD's core symptom domains over time. The McLean Screening Instrument for BPD (MSI-BPD)[4] offers a complementary self-report option. Baseline administration of one of these instruments, with repeat assessment at each monitoring visit, transforms a subjective impression of response into doc-

[3]Zanarini, M. C., Vujanovic, A. A., Parachini, E. A., Boulanger, J. L., Frankenburg, F. R., & Hennen, J. (2003). Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. *Journal of Personality Disorders, 17*(3), 233–242. https://doi.org/10.1521/pedi.17.3.233.22147

[4]Zanarini, M. C., Vujanovic, A. A., Parachini, E. A., Boulanger, J. L., Frankenburg, F. R., & Hennen, J. (2003). A screening measure for BPD: the McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD). *Journal of Personality Disorders, 17*(6), 568–573. https://doi.org/10.1521/pedi.17.6.568.25355

umented, comparable data.

Informed consent. Document the off-label nature of this use, the evidence base and its limitations, risks (including sedation, respiratory depression, physical dependence requiring taper if discontinued, and significantly reduced efficacy of opioid analgesics for pain — see FAQ for clinical implications), alternatives considered, and the patient's understanding and agreement.

Early Titration Phase (First 1–3 Months)

Follow-up should occur at least monthly during titration, with more frequent visits as clinically indicated. The goal is to identify the minimum effective dose while monitoring for adverse effects or concerning patterns.

At each visit, assess for sedation, mood changes (including worsening dysphoria), suicidal ideation, dissociative symptoms if present at baseline, and changes in substance use. Reinforce criteria for urgent contact: new or escalating substance use, significant mood destabilization, respiratory symptoms, or intoxication-seeking behavior.

Dose adjustments should be conservative and guided by documented functional response rather than subjective mood reports alone. Continue PDMP review at each visit; repeat urine drug screening based on individual risk.

In the event a patient presents to emergency services during the course of treatment, buprenorphine's receptor occupancy affects the efficacy of opioid analgesics and may interact with sedating agents used in crisis settings. Patients should carry written documentation of their buprenorphine use — including dose and indication — for presentation to any emergency or crisis provider.

Ongoing Monitoring (After Stabilization)

Once stable, visit intervals may be extended at clinician discretion but should generally not exceed three months. Continue periodic PDMP review and urine drug screening based on clinical risk.

At each visit, reassess the treatment goals established at baseline — suicidal ideation, crisis utilization, therapy engagement, interpersonal functioning, and substance use. Continued prescribing should remain contingent on demonstrable functional benefit and absence of misuse or diversion.

If meaningful benefit is not observed after an adequate trial (suggested minimum of 8–12 weeks at a therapeutic dose), tapering and discontinuation should be considered.

Duration of Treatment and Reassessment

The optimal duration of treatment for interpersonal and affective dysregulation is unknown. Some patients may require longer-term stabilization; others may find that, after a period of sustained symptom reduction and improved psychosocial functioning, tapering is feasible.

Neuroplastic adaptation in stress and attachment systems is well established in the broader psychiatric literature. It is plausible that reduced crisis cycling and improved relational stability may allow endogenous regulatory systems to recalibrate over time.

However, no prospective data currently define a timeline for such change in this context.

For this reason, continued treatment should remain contingent on demonstrable functional benefit. Periodic, structured reassessment of ongoing need is recommended, and gradual taper trials may be considered when stability has been sustained.

In some cases, transition to alternative modulatory approaches (e.g., very-low-dose naltrexone) may be explored after stabilization, though comparative data are lacking.

Tapering and Discontinuation

Discontinuation may be indicated by inadequate response after an adequate trial, significant adverse effects, medication misuse or diversion, emergence of uncontrolled substance use disorder, or patient request. Where the patient is benefiting but clinical complexity exceeds the prescriber's comfort level, referral for co-management is appropriate and should not be framed as treatment failure.

When discontinuation is indicated or requested, gradual taper is preferable to abrupt cessation. Physical dependence can occur even at low doses, and some patients experience mild withdrawal even at the lower end of the dose range used in this context. Formal tapering protocols for this dose range have not been established — SAMHSA's TIP-63 acknowledges that no ideal tapering protocol exists even for OUD doses, and guidance for sub-OUD doses is essentially absent from the literature. A gradual stepwise reduction is a reasonable precaution. Monitoring should increase during any taper attempt, and psychosocial support should be reinforced where possible.

Patients with BPD may have limited insight into certain symptoms — particularly interpersonal patterns such as splitting and idealization/devaluation — making self-report an unreliable sole indicator of recurrence during or after taper. Patients who have stabilized on buprenorphine may also attribute their improvement to other concurrent changes in their life or health, and may underestimate the medication's contribution when considering discontinuation. Prospective monitoring using a structured outcome measure (see Section 7.2, Baseline Assessment) during and after taper can identify recurrence earlier than subjective report alone.

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8. Contraindications and Cautions

- **Active uncontrolled substance use disorder (other than when treating OUD):** Patients with active, chaotic polysubstance use present significant risk management challenges. Consider addiction medicine consultation before proceeding.
- **Concurrent benzodiazepine use:** As noted above, this combination carries respiratory depression risk. It is not an absolute contraindication but requires explicit risk documentation and should prompt a careful benefit–risk discussion.
- ⚠ **Concurrent naltrexone use:** Naltrexone — including low-dose naltrexone (LDN) formulations — is **absolutely contraindicated** in patients receiving

buprenorphine. As a full opioid antagonist, naltrexone will displace buprenorphine from mu-opioid receptors and precipitate acute withdrawal. Patients on oral naltrexone (including LDN) should discontinue and allow at least 48–72 hours before buprenorphine is initiated. Patients on extended-release injectable naltrexone (Vivitrol) require a washout of up to 4 weeks aligned with the remaining injection cycle, and transition planning in these cases warrants careful coordination. Clinicians should verify that patients are not prescribed any naltrexone formulation and counsel patients explicitly not to initiate it while on buprenorphine. If naltrexone is being considered for another indication, an alternative must be selected.

- **Pregnancy:** Standard obstetric guidance regarding opioid prescribing applies. Buprenorphine is used in pregnancy for OUD (and is preferred over methadone by some guidelines), but off-label use for interpersonal and affective dysregulation in pregnancy requires obstetric collaboration and heightened scrutiny. Neonatal opioid withdrawal syndrome (NOWS) is a known risk of prenatal opioid exposure and should be discussed explicitly with the patient and the obstetric team.
- **Clinic policy restrictions:** Some primary care settings have institutional policies regarding controlled substance prescribing that may limit this approach. Clinicians should be familiar with their practice's policies and seek administrative clarity where needed.
- **Absence of psychiatric engagement:** Traditionally, opioid prescribing for psychiatric indications has been reserved for patients already engaged in psychotherapy and psychiatric care. However, treatment refusal and difficulty maintaining therapeutic relationships are themselves features of severe BPD, often driven by the interpersonal dysregulation that buprenorphine may address. In cases where a patient has been unable to engage with or benefit from psychotherapy due to affective intensity, and where the PCP has an established therapeutic relationship, initiating buprenorphine as a bridge to future psychiatric engagement may be reasonable. Document the rationale clearly, establish close follow-up, and maintain active attempts to connect the patient with mental health resources. Buprenorphine is not a substitute for long-term psychiatric care, but it may create the neurobiological conditions under which such care becomes accessible.

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9. Potential Primary Care Benefits

When effective, interpersonal and affective stabilization via buprenorphine may produce the following clinically meaningful outcomes:

- **Reduced crisis escalation:** Fewer acute decompensations requiring ER visits or crisis intervention
- **Improved emotional proportionality:** Responses to interpersonal stressors that are better calibrated to the nature and severity of the event

- **Improved continuity of care:** More consistent appointment attendance and therapeutic engagement, as interpersonal crises are one of the primary drivers of care fragmentation in this population
- **Improved psychotherapy efficacy:** DBT and related approaches require patients to access and use skills during moments of distress; reduction in peak affect intensity may improve the window in which skills are accessible
- **Reduced reliance on maladaptive regulatory behaviors:** Self-injury, substance use, or other high-intensity behaviors may decrease as the neurobiological need for opioid surges is reduced
- **Reduced ER utilization:** If crisis cycling decreases, downstream healthcare utilization may decrease as well — a meaningful outcome for patients, systems, and payers

These outcomes should be monitored prospectively and documented. In the absence of clear benefit after an adequate trial (suggested minimum: 8–12 weeks at therapeutic dose), reassessment and likely discontinuation is appropriate.

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10. When Referral May Be More Appropriate

Buprenorphine for interpersonal and affective dysregulation is an advanced and off-label application. Referral should be strongly considered when:

- **Addiction medicine:** The patient has active or complex substance use history, or the prescribing clinician is uncertain about diversion risk, misuse potential, or appropriate monitoring intensity.
- **Pain medicine:** Chronic pain is a prominent comorbidity and has not been adequately evaluated or managed. A pain specialist may better characterize the nociceptive component and whether buprenorphine's analgesic properties are an appropriate fit.
- **Psychiatry with buprenorphine experience:** Increasingly, psychiatrists with psychopharmacology expertise and buprenorphine prescribing experience are positioned to manage this kind of complex, off-label application. If such a clinician is available, co-management or direct referral is preferred for complex presentations.

Referral is not a failure. In many cases, the PCP's role is to recognize the clinical picture, initiate the conversation, and connect the patient to appropriate specialist resources.

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11. Having the Conversation with Your Patient

Introducing buprenorphine to a patient with BPD for interpersonal and affective — rather than addiction-related — reasons requires thoughtful framing. Patients may have complicated feelings about opioid medications, a history of substance use (their own or in their family), or previous experiences of being undertreated or dismissed.

The following language may be adapted as appropriate:

"There's a medication called buprenorphine that's most commonly used for opioid addiction, but at doses well below what's used for addiction, it's being studied for something different — helping to stabilize the part of your nervous system that's involved in connection and relationships. The research shows that in conditions like yours, there may be lower-than-normal activity in a system in the brain that regulates how we experience closeness, separation, and emotional pain related to other people. When that system is running low, small interpersonal stressors can feel overwhelming, and your emotional reactions can be more intense than the situation calls for. Buprenorphine, at these lower doses, may help bring that system back into balance — not by numbing you or changing your personality, but by making those intense reactions more proportional. It's not a cure, and it's not a replacement for the work you're doing in therapy. But for some people, it may help make that work more accessible. I want us to think through whether it might make sense to try, and what that would look like."

Key principles for this conversation:

- **Lead with mechanism and connection, not stigma:** Frame buprenorphine in terms of what it does neurobiologically — particularly its role in the attachment and social pain systems — not what it's typically prescribed for. Many patients will respond better to "it affects the system in your brain related to relationships and connection" than to "it's a drug used for addiction."
- **Acknowledge complexity:** Patients with BPD are often attuned to dismissal or oversimplification. Acknowledge that the evidence is early and that you're making this decision together.
- **Address substance use history directly:** If the patient has a history of substance use, address it proactively rather than letting it become an unspoken concern. Discuss what monitoring will look like and why.
- **Set clear expectations:** This is a trial, not a commitment. Establish the evaluation period and what "working" will look like before you start.
- **Validate the interpersonal experience:** Many patients with BPD have been told their reactions are "too much" or "irrational." Framing this as a neurobiological issue — not a character flaw — can be therapeutic in itself.

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12. Frequently Asked Questions

How does treatment with buprenorphine interact with DBT or other psychotherapy?

Buprenorphine is not a substitute for psychotherapy and should not be framed as one. DBT and related structured approaches remain the evidence-based foundation for BPD treatment.

That said, DBT's own biosocial theory explicitly acknowledges a biological contribution to emotional dysregulation — heightened sensitivity and reactivity that makes skill use harder at moments of peak distress. Buprenorphine, in this framework, may act

on the biological substrate that DBT identifies but does not pharmacologically target, potentially widening the window within which skills remain accessible. Whether this translates into measurably improved DBT outcomes has not been studied; no trials have examined DBT in patients receiving buprenorphine for this indication. This represents a meaningful gap in the literature.

In practice, patients who cannot yet access or sustain psychotherapy engagement due to interpersonal dysregulation intensity may find that pharmacological stabilization makes that engagement more achievable. Buprenorphine is not a replacement for the work — it may, for some patients, make the work possible.

"Isn't this just treating BPD with opioids?"

The hypothesis is not that opioids treat a personality disorder. Rather, buprenorphine has a unique pharmacologic profile — partial μ-receptor agonism with high receptor affinity and κ-receptor antagonism — that may stabilize a dysregulated endogenous opioid system involved in attachment, social pain, and stress responsivity.

At sub-OUD doses, receptor occupancy provides steady, partial μ-receptor activation and κ-receptor antagonism, which may modulate stress-linked dysphoria and affective volatility. The goal is stabilization of a dysregulated attachment- and stress-linked regulatory system.

Physical dependence is expected with sustained μ-opioid receptor exposure, even at low doses. However, physical dependence is not synonymous with addiction. Addiction involves compulsive use despite harm, impaired control, and craving-driven behavior. At the low doses described here, buprenorphine's reinforcing properties appear substantially attenuated relative to full-agonist opioids. Structured monitoring remains essential, but the risk profile differs meaningfully from traditional opioid therapy.

Abrupt discontinuation may produce withdrawal symptoms, which are typically milder than those seen at OUD treatment doses. For this reason, discontinuation should involve a gradual taper. As with all off-label applications, transparent discussion of risks, uncertainties, and alternatives is essential.

"Why not use opioid antagonists like naltrexone or naloxone?"

Opioid antagonists such as naltrexone have been studied in self-injury and dissociative symptoms with mixed results. Higher doses (e.g., 50 mg) may reduce self-injury in some patients through μ-opioid receptor blockade, though this mechanism also blocks endogenous opioid signaling and may worsen dysphoria in others.

Low-dose naltrexone (<4.5 mg) is hypothesized to increase endogenous opioid tone through transient μ-receptor blockade, but its effects are intermittent and do not affect κ-receptors at this dose. In contrast, low-dose buprenorphine provides continuous partial μ-agonism and κ-antagonism, which may offer more stable modulation of dysphoria and suicidality. Direct comparative studies are lacking.

"What about addiction risk?"

This is a legitimate concern and should be addressed directly. Buprenorphine's partial

agonism and ceiling effect reduce reinforcing properties and respiratory risk compared to full opioid agonists. In psychiatric applications, dosing is below standard OUD treatment ranges, but misuse risk is not eliminated. Careful patient selection remains essential. Patients with active or recent substance use disorders require individualized risk assessment, and some will not be appropriate candidates. PDMP checks, baseline urine drug screening when indicated, structured follow-up, and clear documentation are appropriate mitigation strategies.

"Can my patient use opioids for pain while on buprenorphine?"

Standard opioid analgesics may have significantly attenuated or absent effect in patients receiving buprenorphine, due to its high binding affinity and receptor occupancy at the mu-opioid receptor. This is an important practical consequence that should be addressed at initiation. Non-opioid and multimodal analgesic strategies should be the default for pain management in this population.

For unplanned acute pain or emergency situations, patients should carry written documentation of their buprenorphine use for presentation to emergency or surgical providers, who may be unfamiliar with this off-label indication. Early anesthesia consultation is essential for any anticipated surgical procedure.

In planned surgical settings where opioid analgesia will be needed, temporary discontinuation via a supervised taper prior to the procedure may be considered. The lower doses used in this context — compared to OUD dosing — allow for a relatively rapid and well-tolerated taper. This approach is not appropriate for patients using buprenorphine for opioid use disorder, where discontinuation carries substantial relapse risk.

"What if the patient escalates dose or requests increases?"

Dose escalation requests are clinically meaningful information, not automatically a problem. In some cases, they reflect undertreated symptoms — as the published case report illustrates, some patients with more severe presentations do require careful titration above the typical low-dose range to achieve functional stabilization. In others, escalation requests may signal emerging misuse or tolerance. The key is to have established clear parameters at the outset — documenting the target dose range and the criteria for reassessment — so that escalation requests can be evaluated within a structured framework rather than reactively. Increases should be guided by observable functional endpoints, not subjective distress alone. If escalation requests are persistent or concerning, referral to addiction medicine or psychiatry is appropriate.

"What about the patient who has been told they can't have controlled substances?"

Prior decisions about controlled substance access may have been made in different clinical contexts, by different providers, or without full information about the patient's BPD diagnosis and its relationship to their pain or affect. These decisions deserve review rather than automatic continuation. However, if there is an active controlled substance agreement that excludes opioids, any prescribing decision must occur within that framework, and renegotiation of the agreement — with documentation — is required before proceeding.

"How do I explain this to a patient who is skeptical of medication?"

Many patients with BPD have been through numerous medication trials with limited benefit, and medication skepticism is often rational given that history. Validate this experience explicitly. Emphasize that this approach is different in mechanism from antidepressants or mood stabilizers — it targets the attachment and social pain system, which other medications don't address — that it uses very low doses (well below what's used to treat addiction), that the trial is time-limited, and that their observations about how they feel will actively guide the decision to continue or stop. Positioning the patient as an expert observer of their own experience — which DBT also emphasizes — can increase engagement.

"Why would buprenorphine work when SSRIs and mood stabilizers haven't?"

SSRIs, mood stabilizers, and antipsychotics modulate serotonin, dopamine, and other neurotransmitter systems, but they do not directly target the endogenous opioid system. If the core dysregulation in BPD is in the opioid-mediated attachment and social pain system — as the evidence increasingly suggests — then it's not surprising that medications acting on other systems would have limited efficacy. Buprenorphine addresses a different neurobiological substrate. This doesn't guarantee it will work, but it explains why prior treatment failures don't predict buprenorphine response.

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13. Evidence Summary

The evidence base for this application is limited and should be represented honestly to patients and colleagues.

Endogenous opioid system and BPD: Research by Barbara Stanley and colleagues on the neuropeptide model of BPD ("The Interpersonal Dimension of Borderline Personality Disorder: Towards a Neuropeptide Model") provides a theoretical and empirical foundation for this approach and explicitly suggests that buprenorphine be investigated for BPD treatment. Bandelow's work ("Borderline Personality Disorder: A Dysregulation of the Endogenous Opioid System?") further characterizes the relationship between reduced opioid tone and the clinical features of BPD, including the self-injury literature implicating endogenous opioid release as a regulatory mechanism.

Buprenorphine and suicidality: The Yovell et al. (2015) randomized controlled trial ("Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation") is the strongest available controlled clinical evidence. The post-hoc BPD subgroup finding — showing particularly robust response compared to placebo — is notable but should be interpreted with caution given its unplanned nature. Supplementary support comes from Stanley et al. (2010), which measured CSF endogenous opioid levels in Cluster B personality disorder patients and found significantly reduced beta-endorphin and met-enkephalin in those with NSSI histories — directly implicating opioid deficiency in self-injurious behavior and concluding that opioid-system pharmacotherapy warrants investigation. That paper also cites postmortem evidence (Gross-

Isseroff et al., 1990) of increased mu-opioid receptor density in suicide victims, suggesting receptor upregulation in response to chronic endogenous opioid insufficiency.

Buprenorphine for BPD: A published case report ("The Use of Buprenorphine/Naloxone to Treat Borderline Personality Disorder") describes an opioid-naive BPD patient stabilized on buprenorphine/naloxone at 6 mg following stepwise titration from 2 mg, with cessation of crisis calls as the functional endpoint. This represents the only published clinical report specifically targeting BPD — rather than suicidality — as the primary indication. While a single case cannot establish efficacy or generalizability, it extends the observable clinical range, demonstrates that some patients may require titration above ultra-low doses, and documents a pragmatic approach using commercially available tablet strengths. It should be weighted accordingly: as the most direct available clinical observation for this specific application, while remaining far below the evidentiary threshold of controlled trial data.

κ-opioid receptor and dysphoria: The basic science literature on κ-opioid signaling, stress, and negative affect (Carlezon, Bruchas, and collaborators) provides mechanistic support for the anti-dysphoric properties of buprenorphine's κ-antagonism, though this work is largely preclinical.

Chronic pain and BPD comorbidity: Substantial epidemiological literature documents the high comorbidity of chronic pain conditions with BPD, supporting the dual-indication framing in Scenario B.

Attachment and opioid neurobiology: The broader literature on opioid signaling in social bonding and separation distress (Panksepp and others) provides the foundational framework for understanding BPD as a disorder of the interpersonal regulatory system.

What is not yet available: Prospective trials specifically designed to test buprenorphine for interpersonal and affective dysregulation in BPD, with interpersonal and affective outcomes as primary endpoints, across a range of doses. This gap means that current prescribing in this area is necessarily off-label and hypothesis-driven. Clinicians who choose to use this approach are encouraged to track outcomes prospectively within their own practices and, where appropriate, consider contributing de-identified case reports or case series to the academic literature. Systematic documentation will be essential to clarifying safety, optimal dosing, duration of treatment, and long-term outcomes.

This document was prepared for clinician education purposes. It does not constitute a clinical protocol or standard of care. Prescribers assume individual responsibility for clinical decisions made in their practice.